REMARKS

Claims 256 and 257 have been amended to more distinctly claim that which Applicants regard as their invention. As will be discussed below, amended claims 256 and 257 are supported by the specification.

The Rejection for Double Patenting

Claims 255, 257 and 259 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 245-247 of copending Application No. 08/978,632. In the December 19, 2000 Office Action (page 2), the Examiner stated that "[a]lthough the conflicting claims are not identical, they are considered not to be patentably distinct from each other for the same reasons of record as stated in the first Official actions mailed 02/16/99 and 11/09/99."

The double patenting rejection will be addressed upon indication of allowable subject matter.

The Rejection Under 35 U.S.C. 112, Second Paragraph

Claims 256-260 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In a previous Office Action, the Examiner stated:

> The examples taught in the specification do not clarify the metes and bounds of "specific complex" in terms of the "non-covalent binding" which comprises the specific complex. Neither the claims nor the specification clarify how the "non-covalent binding" comprises

> a "specific complex" such as "is mediated by a ligand binding receptor" (as in claim 257). The examples taught in the specification don't teach how a ligand binding receptor "mediates" the "specific complex" as claimed such as in the Markush groups in claim 258 which include binding pairs not even containing a receptor as a part of the pair. For instance, it is not clear from the language of the claims whether the non-covalent binding is comprising the ligand/receptor interaction and thus whether the specific complex is the ligand/receptor interaction. If so, claim 258 is clearly indefinite for claiming "said ligand binding receptor" as selected from groups having interactions such as antigen/antibody interactions and other such interactions that do not comprise a receptor interaction. In summary, neither the specification, the claims nor applicant's arguments have addressed the metes and bounds of the claimed "specific complex" in relation to the non-covalent binding it comprises and more specifically, in view of the unclear relationship "wherein said specific complex is mediated by a ligand binding receptor (claim 257)."

In response, Applicants have amended claims 256 and 257. Claim 256 now recites that the domains are attached noncovalently through specific binding. Examples of noncovalent specific binding are provided on pages 53 and 54. For example, on page 53, there is a section on useful domains with specific cell binding properties. Page 54 provides examples of useful domains with specific nucleic acid component binding properties. Claim 257 has been amended to recite that the specific binding is mediated by a ligand binding receptor. Examples of "a ligand binding receptor" are provided on page 56, lines 11-21:

> The ligand binding receptor can itself take a number of forms. Suitable but not necessarily limited to these members are a polynucleotide sequence to be recognized by its complementary sequence; an antigen to be recognized by its corresponding antigen;a lectin to be recognized by its corresponding sugar; a hormone to be recognized by its receptor; a receptor to be recognized by its hormone; an inhibitor to be recognized by its enzyme; an enzyme to be recognized by its inhibitor; a cofactor to be recognized by its cofactor enzyme binding site; a cofactor enzyme binding site to be recognized

by its cofactor; a binding ligand to be recognized by its substrate; or a combination of the foregoing.

To clarify claim 258 and as disclosed on page 56, lines 11-21, the ligand binding receptors are deemed to be a polynucleotide sequence, an antigen, an antibody, a lectin, a hormone, receptor, an enzyme inhibitor, an enzyme, a cofactor, a cofactor enzyme a binding ligand. Applicants do note that the claims are interpreted in light of the specification and the inventor may be his own lexicographer so long as the words as he uses are clearly defined in the specification, *Hybritech Incorporated v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986).

In view of the amendments to claims 256 and 257 and the foregoing remarks, Applicants respectfully assert that the rejection under 35 U.S.C. §112, second paragraph has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn upon further consideration.

The First Rejection Under 35 U.S.C. 112, First Paragraph

Claims 245-302 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Furthermore, it is asserted that Applicant does not further address the enablement of the claimed constructs applied to whole organisms as broadly claimed. The Examiner's remarks on set forth in the Office Actions mailed 2/16/99 and 11/09/99.

Applicants respectfully traverse the rejection. First, Applicants note that claims 245-262, 266-280, 284-298 and 302 are directed to compositions and kits, not to a method. Therefore, the issue of whether or not the use of the claimed

compositions or kits is enabled only in vitro or in vivo is not determinative under the standard applied pursuant to 35 U.S.C. §§101 or 112, first paragraph, given that it is acknowledged in the Office Action that Applicants have provided examples that show antisense inhibition of HIV in infected U937 cell culture using various U1 constructs, expression of A, B and C antisense by hybridization analysis after expression of the U1 clone, and expression of the fusion product antisense A upstream of β-gal gene where antisense activity of the A portion cause inhibition of B-gal activity in lacZ assays (Figure 51).

Claims 263-265, 281-283 and 299-301 are directed to a process for introducing a nucleic acid component into a cell, where the independent claims do not specify whether the component is introduced in vivo or ex vivo. The Office Action dated 8/16/99 states that there is a high level of unpredictability in the antisense art and analogous gene therapy art for in vivo (whole organism). In the Examiner's view, barriers to successful delivery of antisense to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus (2) withstanding enzymatic degradation and (3) the ability to find and bind the target site and simultaneously avoiding non-specific binding. The Office Action cites passages from Branch and Flanagan as evidence of skepticism of those of skill in the art.

In response, Applicants note that Branch and Flanagan were actually published *after* the priority date of the above-referenced application. The MPEP in Section 2164.05(a) states that "the state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date." This section further states "In general, the examiner should not use post-filing date references to demonstrate that the patent is no-enabling." Applicants nevertheless assert that there are a number of publications available as

of the priority date of the above-referenced application as well as publications published after the priority date of the above-referenced application which express a more optimistic attitude regarding the suitability of antisense to become useful in therapeutic application. One example of such a publication is Crooke, 1994, Antisense Research and Development 4:145-6, attached hereto as Exhibit 1. Another example is Liu et al., 1997, J. Virol. 71:4079-4085, attached hereto as Exhibit 2, which shows that Tat-activated expression of chloramphenicol acetyltransferase was specifically inhibited in cells expressing Tat and transactivation response region antisense sequences.

It is also Applicants' position that *in vivo* data is not necessary. As noted in the MPEP Section 2107.03, III, "Office personnel should be careful not to find evidence unpersuasive simply because no animal model for the human disease condition had been established prior to the filing of the application." Applicants note, however, that clinical trials were underway by the assignee of the instant application around the priority date of the above-referenced application. A press release dated July 1, 1996 is attached hereto as Exhibit 3. The results to date have been favorable and several public announcements regarding the Assignee's clinical trials have been made.

Applicants would also like to respond to other points raised in the Office Action. First, as conceded in the Office Action, Applicants have demonstrated the penetration of cells by the antisense compounds, notably antisense inhibition of HIV in infected U937 cell culture. Therefore, the question of penetration of the plasma membrane of target cells should not be an issue.

Second, Applicants note that specificity to any degree and certainly 100% specificity is not required of any drug under the patent laws and is evaluated on a case-by-case basis by the Food and Drug Administration. For example, penicillin is

known to be far from specific to a certain target protein of harmful bacteria. However, this does not diminish the importance of penicillin as a useful drug.

In view of the foregoing remarks and attached exhibits (1-2), Applicants respectfully request reconsideration and withdrawal of the enablement rejection.

The Rejections Under 35 U.S.C. 112, First Paragraph-Written Description

Claims 245-262, 267-280 and 285-298 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. It is asserted that the specification as filed teaches only prophetically the majority of the constructs for the breadth claimed, and does not clearly describe to one skilled in the art that the inventor was in possession of the genus of claimed constructs considering the high level of unpredictability in the gene therapy and antisense art, the suggested applications for the prophetic constructs taught for producing a product in a cell, such as antisense.

Applicants respectfully traverse the rejection. The Final Written Description Guidelines state in Paragraph II.A.3.a:

> Possession may be shown in many ways. For example, possession may be shown, inter alia, by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention.....

An applicant may show possession of an invention by disclosure of drawings \39\ or structural chemical formulas\40\ that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. The description need only describe in detail that which is new or not conventional.\41\ This is equally true whether the claimed invention is directed to a product or a process.
An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics \42\ which provide evidence that applicant was in possession of the claimed invention,\43\ i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.\44\ What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.\45\ If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.\46\

The Written Description Guidelines further state in paragraph II.A.3.a.(2)

(2) For each claim drawn to a genus:
The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice ....., reduction to drawings ....., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (citiation omitted).
A ``representative number of species'' means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. On the other hand, there may be situations where one species adequately supports a genus (citation omitted). What

> constitutes a ``representative number'' is an inverse function of the skill and knowledge in the art.
> Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus (citation omitted).
> Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces (citation omitted). If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description under 35 U.S.C. 112, para. 1.

Applicants assert that an adequate description has been provided. A detailed description of the constructs of the present invention are provided throughout the specification. For example, the last paragraph of page 47 in their specification states:

> Another significant embodiment of the present invention is a construct which when present in a cell produces a product, the construct being bound non-ionically to an entity comprising either a chemical modification or a ligand addition, or both. As in the case of the other above-described construct, this construct may also comprise at least one terminus, such terminus comprising a polynucleotide tail. The polynucleotide tail is hybridizable or hybridized to a complementary polynucleotide sequence. An antibody to a double stranded nucleic acid can be directed and thus bound to such hybridized polynucleotide tail sequences. The antibody can comprises a polyclonal antibody or a monoclonal antibody.

A detailed description of the compositions of the present invention are provided on pages 48-59. The terms "nucleic acid component", "domain", and "binder" are clearly defined on pages 48-49. Various examples of useful

domains are also described. These include useful domains with non-specific cell binding properties (see page 53), useful domains with specific cell binding properties (see page 53), useful domains with specific nucleic acid component binding properties (see page 54). Examples of various binders are provided on page 55. Specific examples of the constructs and compositions of the present invention are shown in Examples 12-15. Accompanying figures are provided specifically in Figures 16-20.

The disclosures in the specification clearly conform to the Written Description guidelines. A depiction of the invention has certainly been provided in Figures 16 and 17. Applicants note that three cases are cited in footnote 39 pertaining to the use of drawings pertaining to the adequacy of the Written Description Requirement. Specifically, footnote 39 states:

> See, e.g., *Vas-Cath*, 935 F.2d at 1565, 19 USPQ2d at 1118 (``drawings alone may provide a `written description' of an invention as required by Sec. 112''); *In re Wolfensperger*, 302 F.2d 950, 133 USPQ 537 (CCPA 1962) (the drawings of applicant's specification provided sufficient written descriptive support for the claim limitation at issue); *Autogiro Co. of America v. United States*, 384 F.2d 391, 398, 155 USPQ 697, 703 (Ct. Cl. 1967) (``In those instances where a visual representation can flesh out words,drawings may be used in the same manner and with the same limitations as the specification.'').

Sufficient identifying characteristics of the constructs, compositions and kits of the present invention is provided as noted above in the specification. Additionally, a sufficient number of species have been disclosed. Finally, Applicants note that actual reduction to practice is not required to satisfy the Written Description Requirement. Footnote 36 of Written Description Guidelines state

> ....."The word 'invention' must refer to a concept that is complete, rather than merely one that is 'substantially complete.' It is true that reduction to practice ordinarily provides the best evidence that an invention is complete. But just because reduction to practice is sufficient evidence of completion, it does not follow that proof of reduction to practice is necessary in very case. Indeed, both the facts of the *Telephone Cases* and the facts of this case demonstrate that one can prove that an invention is complete and ready for patenting before it has actually been reduced to practice.

Therefore, the claimed invention is adequately described.

In view of the above arguments, Applicants assert that the rejection at hand has been overcome. Applicants respectfully request, therefore, that the second rejection under 35 U.S.C. 112, first paragraph be withdrawn.

The Rejections Under 35 U.S.C. 102(e)

Claims 245-302 stand rejected under 35 U.S.C. §102(e) as being anticipated by Curiel et al , U.S.Patent 5,521,021 (hereinafter "Curiel"). It is asserted that the broad scope of the instant claims reads on virtually any nucleic acid construct for expression of a product in a cell. In the Examiner's view, Curiel teaches constructs falling within the scope of the invention as broadly claimed. It is therefore not clear to examiner how the constructs taught by Curiel et al. would be considered to lack material identity for the breadth of possible constructs instantly claimed.

Applicants respectfully traverse the rejection. Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Foundation v. Genentech Inc.* 927 F.2d 1565, 18 USPQ2d 1001, 18 USPQ2d 1896 (Fed. Cir. 1991).

Applicants assert that the construct recited in claims 245-246 and the compositions and kits recited in the remaining claims can be distinguished from Curiel. Specifically, the construct of the present invention comprises a polynucleotide tail hybridized to a complementary polynucleotide sequence and an antibody bound to said hybridized polynucleotide sequence. In contrast, the adenovirus conjugate does not contain such a polynucleotide tail that hybridizes to a complementary polynucleotide sequence. Specifically, the plasmid in the conjugate of Curiel contains no such terminus, since it is a closed circular DNA. No such purpose of a terminus and tail would be served in such a plasmid. It merely contains an adenovirus capable of endosomolysis bound to an antibody. The antibody is bound to a nucleic acid via a polycation. The nucleic acid component is delivered to the eukaryotic cell.

The composition of the present invention also differs significantly from the adenovirus conjugate of Curiel. The composition of the present invention comprises a non-natural entity containing one domain to a nucleic acid component and at least one domain to a cell of interest and the nucleic acid component. In contrast, the adenovirus of Curiel does not contain all three of the elements of the composition claimed in claim 247. The conjugate of Curiel contains the adenovirus which binds to the cell and thus may be considered the domain to a cell of interest. The antibody bound to the adenovirus does not bind to the cell of interest via a polycation. The antibody is also bound to a the nucleic acid introduced into the cell. Therefore, it may be concluded that the conjugate disclosed by Curiel does not contain a domain to the nucleic acid component.

To better illustrate the differences between the compositions and constructs of the present invention and the adenovirus conjugates of Curiel, Applicants attach hereto Figures 16 and 17 of the instant application and Figure 1 of Curiel. As

noted in the text (see Examples 13-15). All of these examples disclose using an inactivated adenovirus bound to a bispecific antibody in order to facilitate cellular uptake of the complex. In Example 13, single stranded DNA is attached to the antibody. This single stranded DNA hybridizes to adeno associated virus, which could be used as a vector. In Examples 14-15, The DNA contains lactyl groups which bind to the cell. Clearly, the adenovirus conjugate of Curiel et al. does not contain a DNA linker, a domain to a nucleic acid component.

In view of the above arguments and amendments, Applicants assert that the rejection of the claims under 35 U.S.C. §102(e) over Curiel et al. be withdrawn.

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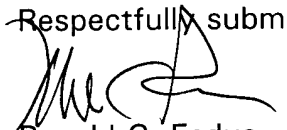
SUMMARY AND CONCLUSIONS

Claims 245-302 are presented for further examination. Claims 256 and 257 have been amended. No claims have been added by this paper.

No claim fee or other fees are believed due in connection with this response. In the event that any fee is due for this paper or any paper being filed in connection with the accompanying Petition, however, The Patent and Trademark Office is authorized to charge any such fee or fees to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,



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MARKED UP VERSION OF THE CLAIMS

247. (Amended) A composition comprising:

(a) a non-natural entity which comprises:

at least one domain to a specific nucleic acid component; and

at least one domain to a cell of interest; and

(b) said specific nucleic acid component; wherein the domain or domains to said nucleic acid component are different from the domain or domains to said cell.

257. (Amended) The composition of claim [256] 247, wherein said specific [complex] binding is mediated by a ligand binding receptor.

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